

Curriculum Vitae

RICHARD S. GEARY, Ph. D.

EDUCATION:

Ph.D., Pharmaceutics, University of Texas at Austin, 1988
B.S., Biology, Texas A&M University, 1980

PROFESSIONAL POSITIONS AND EXPERIENCE:

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| 2008-Present | Senior Vice President of Development, Isis Pharmaceuticals
<i>Job Description:</i> Responsible for preclinical and clinical development of antisense drugs. |
| 2003-2008 | Vice President of Pharmacokinetics and Metabolism, Isis Pharmaceuticals, Department of Toxicology and Pharmacokinetics
<i>Job Description:</i> Provide direction and support for preclinical and clinical development of oligonucleotide therapeutics. |
| 2001-2003 | Executive Director of Pharmacokinetics, Isis Pharmaceuticals, Department of Toxicology and Pharmacokinetics |
| 1998-2001 | Director of Pharmacokinetics, Isis Pharmaceuticals, Department of Toxicology and Pharmacokinetics |
| 1997-1998 | Associate Director of Pharmacokinetics, Isis Pharmaceuticals, Department of Toxicology and Pharmacokinetics |
| 1995-1997 | Assistant Director of Pharmacokinetics, Isis Pharmaceuticals, Department of Toxicology and Pharmacokinetics |
| 1993-1995 | Manager, Southwest Research Institute, Applied Biopharmaceutics and Physical Chemistry, Department of Applied Chemistry and Chemical Engineering |
| 1992-1993 | Group Leader, Southwest Research Institute, Pharmaceutics and Pharmacology Section, Department of Applied Chemistry and Chemical Engineering |
| 1990-1992 | Senior Research Scientist, Southwest Research Institute, Pharmaceutics and Pharmacology Section, Department of Applied Chemistry and Chemical Engineering |

1987-1990 Research Scientist, Southwest Research Institute, Pharmaceuticals and Pharmacology Section, Department of Applied Chemistry and Chemical Engineering

CONTINUING EDUCATION COURSES:

Incorporation of Pharmacokinetic and Pharmacodynamic Data into Risk Assessment, Nashville, TN, SOT, 2002

Prediction of Human Toxicity and Metabolic Fate of Drugs Using In Vitro Systems, San Francisco, CA, SOT, 2000

Advances in Non-Invasive Micrometer and Nanometer Scale Cellular/Tissue Vital Imaging, Philadelphia, PA, SOT, 2000

Toxicokinetics and Physiologically-Based Toxicokinetics in Toxicology and Risk Assessment, Philadelphia, PA, SOT, 2000

Advanced Topics in Toxicokinetics, Anaheim, CA, SOT, 1996

New Approaches for Studying Cytochrome P450-Dependant Toxicant Metabolism, Anaheim, CA, SOT, 1996

Application of Pharmacokinetics to Toxicological Testing, Dallas, TX, SOT, 1994

Implementing PBPK Models, Dallas, TX, SOT, 1991

Introduction to Physiologically-based Pharmacokinetic Modeling, Dallas, TX, SOT, 1991

TRAINING COURSES:

Understanding GLP's (Video), 1998

Short Course in Population Pharmacokinetics Data Analysis using the NONMEM System, April 20-22, 1998

Performance Management and Appraisal Training Program – The Coach Approach, 1997

Population Pharmacokinetics and P-Pharm Workshop, April 1-3, 1996

GLP Training – SwRI 1992-1995

Total Quality Management – SwRI 1993

One-week Workshop on Advanced Methods in Pharmacokinetics/Pharmacodynamics, April 1-6, 1990

BOOKS AND CHAPTERS:

Bennett, C. F., Swayze, E., Geary, R., Henry, S., Tillman, L., Hardee, G. (2008) Antisense Oligonucleotide-based Therapeutics. *Gene and Cell Therapy: Mechanisms and Strategies*. 497-522

Yu, R. Z., Geary, R. S., and Levin, A. A. (2007). Pharmacokinetics and Pharmacodynamics of Antisense Oligonucleotides. In *Encyclopedia of Molecular Cell biology and Molecular Medicine* (R. A. Meyers, ed. Wiley-VCH, Weinheim, Germany.

Geary, R. S., Yu, R. Z., Siwkowski, A., and Levin, A. A. (2007). Pharmacokinetic/Pharmacodynamic Properties of Phosphorothioate 2' - O-(2-Methoxyethyl)-Modified Antisense Oligonucleotides in Animals and Man. In *Antisense Drug Technology, Principles, strategies and applications*. S. T. Crooke, ed., Vol. 2, pp. 305-326. Taylor & Francis Group, Boca Raton, FL.

Hardee, G. E., Tillman, L. G., and Geary, R. S. (2007). Routes and Formulations for Delivery of Antisense Oligonucleotides. In *Antisense Drug Technology, Principles, strategies and applications*. S. T. Crooke, ed., Vol. 2, pp. 217-236. Taylor & Francis Group, Boca Raton, FL.

Levin, A. A., Yu, R. Z., and Geary, R. S. (2007). Basic Principles of the Pharmacokinetics of Antisense Oligonucleotide Drugs. In *Antisense Drug Technology, Principles, strategies and applications*. S. T. Crooke, ed., Vol. 2, pp. 183-215. Taylor & Francis Group, Boca Raton, FL.

Yu, R., Geary, R.S., Watanabe, T., Levin, A.A., Schoenfeld, L.S., Pharmacokinetic properties in humans. *Antisense Drug Technology: Principles, Strategies, and Applications*. (2001) Marcel Dekker, Inc. 183-200.

Geary, R.S., Yu, R., Leeds, J.M., Watanabe, T., Henry, S.P., Levin, A.A., Templin, M.V. Pharmacokinetic properties in animals. *Antisense Drug Technology. Principles, Strategies, and Applications*. (2001) Marcel Dekker, Inc. 119-154.

Bennett, F.C., Butler, M., Cook, D.P., Geary, R.S., Levin, A.A., Mehta, R., Teng, C.L., Deshmukh, H., Tillman, L., Hardee, G. (2000) Antisense oligonucleotide-based therapeutics. *Gene Therapy*. Marcel Dekker, Inc. 305-332.

Levin, A.A., Geary, R.S., Leeds, J.M., Monteith, D.K., Yu, R., Templin, M.V. and Henry, S.P., (1998). The pharmacokinetics and toxicity of phosphorothioate oligonucleotides. *Biotechnology and Safety Assessment*, Taylor & Francis. 1: 151-175.

Levin, A.A., Monteith, D.K., Leeds, J.M., Nicklin, P.L., Geary, R.S., Butler, M., Templin, M.V. and Henry, S.P., (1998). Toxicity of oligodeoxynucleotide therapeutic agents. *Antisense Research and Application*. Crooke, S.T. Heidelberg, Springer. 131: 169-215.

Leeds, J.M. and Geary, R.S., (1998). Pharmacokinetic properties of phosphorothioate oligonucleotides in humans. *Antisense Research and Application*. Crooke, S.T. Heidelberg, Springer. 131: 217-232.

Geary, R.S., (1993). *Drug delivery systems and recombinant proteins*. Biotechnology and Safety Assessment., Raven, New York, NY.

PROFESSIONAL PUBLICATIONS:

Fidias P, Pennell NA, Boral AL, Shapiro GI, Skarin AT, Eder JP Jr, Kwok TJ, Geary RS, Johnson BE, Lynch TJ, Supko JG. Phase I study of the c-raf-1 antisense oligonucleotide ISIS 5132 in combination with carboplatin and paclitaxel in patients with previously untreated, advanced non-small cell lung cancer. *J Thorac Oncol*. 2009 Sep; 4(9):1156-62.

Geary RS. (2009) Antisense Oligonucleotide Pharmacokinetics and Metabolism. *Expert Opinion, Drug Metabolism & Toxicology*. 2009 Apr;5(4):381-91.

Geary RS, Wancewicz E, Matson J, Pearce M, Siwkowski A, Swayze E, Bennett F. (2009) Effect of Dose and Plasma Concentration on Liver Uptake and Pharmacologic Activity of a 2'-Methoxyethyl Modified Chimeric Antisense Oligonucleotide Targeting PTEN. *Biochemical Pharmacology*. 78 (2009) 284-291.

Yu R.Z., Lemonidis K.M., Graham M.J., Matson J.E., Crooke R.M., Tribble D.L., Wedel M.K., Levin A.A., Geary R.S. (2009) Cross-species comparison of In Vivo PK/PD relationships for second generation antisense oligonucleotides targeting apolipoprotein B-100. *Biochemical Pharmacology*. 2009 March, 77 (5) 910-919.

Yu R.Z., Geary R.S., Flaim J., Riley G., Tribble D., van Vliet A., Wedel M. (2009) Lack of Pharmacokinetic Interaction of Mipomersen Sodium (ISIS 301012), a 2'-O-Methoxyethyl Modified Antisense Oligonucleotide Targeting Apolipoprotein B-100 Messenger RNA, with Simvastatin and Ezetimibe. *Clinical Pharmacokinetics*. 2009; 48 (1): 39-50.

Crosby J.R., Guha M., Tung D., Miller D.A., Bender B., Condon T.P., York-Defalco C., Geary R.S., Monia B.P., Karras J.G., Gregory S.A. (2007). Inhaled CD86 Antisense Oligonucleotide Suppresses Pulmonary Inflammation and Airway Hyper-responsiveness in Allergic Mice. *J Pharm Sci*. 2008 Jan; 97 (1): 225-36.

Tillman L.G., Geary R.S., and Hardee G.E. (2007). Oral Delivery of Antisense Oligonucleotides In Man. *J Pharm Sci*. 2008 Jan; 97 (1): 225-36.

Yu R.Z., Kim T.W., Hong A., Watanabe T.A., Gaus H.J., and Geary R.S. (2007). Cross-Species Pharmacokinetic Comparison from Mouse to Man of a Second Generation Antisense Oligonucleotide ISIS 301012, Targeting Human ApoB-100. *Drug Metab. Dispos.* 35, 460-468.

Karras J.G., Crosby J.R., Guha M., Tung D., Miller D.A., Gaarde W.A., Geary R.S., Monia B.P., and Gregory S.A. (2007). Anti-inflammatory activity of inhaled IL-4 receptor-alpha antisense oligonucleotide in mice. *Am J Respir Cell Mol Biol* 36, 276-85.

Geary R.S., Bradley J.D., Watanabe T., Kwon Y., Wedel M., van Lier J.J., vanVliet A.A. (2006). Lack of Pharmacokinetic Interaction for ISIS 113715, a 2'-O-Methoxyethyl Modified Antisense Oligonucleotide Targeting Protein Tyrosine Phosphatase 1B Messenger RNA, with Oral Antidiabetic Compounds Metformin, Glipizide or Rosiglitazone. *Clinical Pharmacokinetics: Volume 45(8)* 2006pp 789-801.

Miner P.B., Jr., Geary R.S., Matson J., Chuang E., Xia S., Baker B.F., and Wedel M.K. (2006). Bioavailability and therapeutic activity of alicaforsen (ISIS 2302) administered as a rectal retention enema to subjects with active ulcerative colitis. *Aliment Pharmacol Ther* 23, 1427-1434.

Watanabe, T.A., Geary, R.S., and Levin, A.A. (2006). Plasma Protein Binding of an Antisense Oligonucleotide Targeting Human ICAM-1 (ISIS 2302). *Oligonucleotides* 16, 169-180.

Soucy, N.V., Riley J.P., Templin, M.V., Geary, R.S., de Peyster, A., and Levin, A.A. (2006). Maternal and fetal distribution of a phosphorothioate oligonucleotide in rats after intravenous infusion. *Birth Defects Res B Dev Reprod Toxicol* 77 (1):22-28.

Chen, W., Langer, R.M., Janczewska, S., Furian, L., Geary, R., Qu, X., Wang, M., Verani, R., Condon, T., Stecker, K., Bennett, C. F., and Stepkowski, S. M., (2005) Methoxyethyl-modified intercellular adhesion molecule-1 antisense phosphorothioate oligonucleotides inhibit allograft rejection, ischemic-reperfusion injury, and cyclosporine-induced nephrotoxicity, *Transplantation* 79 (4): 401-408.

Advani, R., Lum, B.L., Fisher, G.A., Halsey, J., Geary, R.S., Holmlund, J.T., Kwok, T.J., Dorr, F.A., & Sikic, B.I. (2005) A phase I trial of aprinocarsen (ISIS 3521/LY900003), an antisense inhibitor of protein kinase C- α administered as a 24-hour weekly infusion schedule in patients with advanced cancer. *Invest New Drugs*, 23, 467-477.

Albertshofer, K., Siwkowski, A.M., Wancewicz, E.V., Esau, C.C., Watanabe, T., Nishihara, K.C., Kinberger, G.A., Malik, L., Eldrup, A.B., Manoharan, M., Geary, R.S., Monia, B.P., Swayze, E.E., Griffey, R.H., Bennett, C.F. and A., M.M. (2005). Structure-Activity Relationship Study on a Simple Cationic Peptide Motif for Cellular Delivery of Antisense Peptide Nucleic Acid. *J Med Chem.* 2005 Oct 20;48(21):6741-9.

Murphy, A.T., Brown-Augsburger, P., Yu, R.Z., Geary, R.S., Thibodeaux, S. and Ackermann, B.L. (2005). Development of an ion-pair reverse-phase liquid chromatographic/tandem mass

spectrometry method for the determination of an 18-mer phosphorothioate oligonucleotide in mouse liver tissue. *Eur J Mass Spectrom* (Chichester, Eng) 11(2): 209-215.

Villalona-Calero, M.A., Ritch, P., Figueroa, J.A., Otterson, G.A., Belt, R., Dow, E., George, S., Leonardo, J., McCachren, S., Miller, G.L., Modiano, M., Valdivieso, M., Geary, R.S., Oliver, J.W. and Holmlund, J. (2004). A phase I/II study of LY900003, an Antisense inhibitor of protein kinase C- α , in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer. *Clin. Cancer Res.* 10(18 Pt 1): 6086-6093.

Yu, R.Z., Geary, R.S. and Levin, A.A. (2004). Application of novel quantitative bioanalytical methods for pharmacokinetic and pharmacokinetic/pharmacodynamic assessments of antisense oligonucleotides. *Curr Opin Drug Discov Devel* 7(2): 195-203.

Yu, R.Z., Geary, R.S., Monteith, D.K., Matson, J., Truong, L., Fitchett, J. and Levin, A.A. (2004). Tissue disposition of a 2'-O-(2-methoxy) ethyl modified antisense oligonucleotides in monkeys. *J. Pharm. Sci.* 93: 48-59.

Raouf A.A., Chiu P, Ramtoola Z, Cumming I.K, Teng C, Weinbach S.P, Hardee G.E, Levin A.A, Geary R.S. (2004). Oral bioavailability and multiple dose tolerability of an antisense oligonucleotide tablet formulated with sodium caprate. *J Pharm Sci.*:93: (6):1431-1439.

Geary, R.S., Yu, R.Z., Watanabe, T., Henry, S.P., Hardee, G.E., Chappell, A., Matson, J., Sasmor, H., Cummins, L. and Levin, A.A. (2003). Pharmacokinetics of a tumor necrosis factor- α phosphorothioate 2'-O-(2-methoxyethyl) modified antisense oligonucleotide: comparison across species. *Drug Metab. Dispos.* 31(11): 1419-1428.

Yu, R. Z., Su, J. Q., Grundy, J. S., Geary, R. S., Sewell, K. L., Dorr, A., and Levin, A. A. (2003). Prediction of clinical responses in a simulated phase III trial of Crohn's patients administered the antisense phosphorothioate oligonucleotide ISIS 2302: comparison of proposed dosing regimens. *Antisense and Nucleic Acid Drug Development* 13, 57-66.

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Raouf, A.A., Ramtoola, Z., McKenna, B., Yu, R.Z., Greg, H., Geary, R.S. Effect of sodium caprate on the intestinal absorption of two modified antisense oligonucleotide in pigs. *Eur J Pharm Sci*;17(3):131-138, 2002.

Cripps MC, Figueredo AT, Oza AM, Taylor MJ, Fields AL, Holmlund JT, McIntosh LW, Geary RS, Eisenhauer EA. Phase II Randomized Study of ISIS 3521 and ISIS 5132 in Patients with Locally Advanced or Metastatic Colorectal Cancer: A National Cancer Institute of Canada Clinical Trials Group Study. *Clin Cancer Res*;8(7):2188-92, 2002.

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Yu R.Z., Baker B., Chappell A., Geary R.S., Chueng E., Levin A.A. Development of an ultrasensitive noncompetitive hybridization-ligation enzyme-linked immunosorbent assay for the determination of phosphorothioate oligodeoxynucleotide in plasma. *Anal Biochem*. 304:19-25, 2002.

Anthony W. Tolcher, Leonard Reyno, Peter M. Venner, Scott D. Ernst, Malcolm Moore, Richard S. Geary, Kim Chi, Sean Hall, Wendy Walsh, Andrew Dorr and Elizabeth Eisenhauer. (2002) A Randomized Phase II and Pharmacokinetic Study of the Antisense Oligonucleotides ISIS 3521 and ISIS 5132 in Patients with Hormone-refractory Prostate Cancer. *Clinical Cancer Research* Vol. 8, 2530-2535, August 2002.

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Geary, R. S., Yu, R.Z., Levin, A.A. Pharmacokinetics of phosphorothioate antisense oligodeoxynucleotides. *Current Opinion in Investigational Drugs*. 2(4) :562-573, 2001.

Geary, R. S., Khatsenko, O., Bunker, K., Crooke, R., Moore, M., Burckin, T., Truong, L., Sasmor, H., and Levin, A. A. Absolute bioavailability of 2'-O-(2-methoxyethyl)-modified antisense oligonucleotides following intraduodenal instillation in rats. *J Pharmacol Exp Ther* 296(3):898-904, 2001.

Yu, R., Geary, R., Leeds, J., Watanabe, T., Moore, M., Fitchett, J., Matson, J., Burckin, T., Templin, M., and Levin, A. Comparison of pharmacokinetics and tissue disposition of an antisense phosphorothioate oligonucleotide targeting human Ha-ras mRNA in mouse and monkey. *J Pharm Sci* 90(2):182-193, 2001.

Yu, R. Z., Zhang, H., Geary, R. S., Graham, M., Masarjian, L., Lemonidis, K., Crooke, R., Dean, N. M., and Levin, A. A. Pharmacokinetics and pharmacodynamics of an antisense phosphorothioate oligonucleotide targeting Fas mRNA in mice. *J Pharmacol Exp Ther* 296(2):388-395, 2001.

Stepkowski SM, Chen W, Geary R, Wang ME, Condon T, Stecker K, Bennett CF. (2001) Development of an oral formulation for ICAM-1 antisense oligonucleotides. *Transplant Proc.* 2001 Feb-Mar;33(1-2):387. No abstract available.

Rudin CM, Holmlund J, Fleming GF, Mani S, Stadler WM, Schumm P, Monia BP, Johnston JF, Geary R, Yu RZ, Kwoh TJ, Dorr FA, Ratain MJ. (2001) Phase I Trial of ISIS 5132, an antisense oligonucleotide inhibitor of c-ras, administered by 24-hour weekly infusion to patients with advanced cancer. *Clin Cancer Res.* 2001 May;7(5):1214-20.

Stepkowski SM, Chen W, Geary R, Wang ME, Condon T, Stecker K, Bennett CF. (2001) An oral formulation for intracellular adhesion molecules-1 antisense oligonucleotides. *Transplant Proc.* 2001 Nov-Dec;33(7-8):3271.

Khatsenko, O., Morgan, R., Troung, L., York-Defalco, C., Sasmor, H., Conklin, B., Geary, R. Absorption of antisense oligonucleotides in rat intestine: effect of chemistry and length. *Antisense and Nucleic Acid Drug Dev.* 10(1):35-44, 2000.

Geary, R. S., Watanabe, T. A., Truong, L., Freier, S., Lesnik, E. A., Sioufi, N. B., Sasmor, H., Manoharan, M., and Levin, A. A. Pharmacokinetic properties of 2'-O-(2-methoxyethyl)-modified oligonucleotide analogs in rats. *J Pharmacol Exp Ther* 296(3):890-897, 2000.

Cunningham, C. C., Holmlund, J. T., Schiller, J. H., Geary, R. S., Kwoh, T. J., Dorr, A., and Nemunaitis, J. A phase I trial of c-ras kinase antisense oligonucleotide ISIS 5132 administered as a continuous intravenous infusion in patients with advanced cancer. *Clin Cancer Res* 6(5):1626-1631, 2000.

Leeds, J. M., Henry, S. P., Geary, R., Burckin, T., and Levin, A. A. Comparison of the pharmacokinetics of subcutaneous and intravenous administration of a phosphorothioate oligodeoxynucleotide in cynomolgus monkeys. *Antisense Nucleic Acid Drug Dev* 10(6):435-441, 2000.

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Geary, R.S., Matson, J., and Levin, A.A. A Nonradioisotope Biomedical Assay for Intact Oligonucleotide and Its Chain-Shortened Metabolites Used for Determination of Exposure and Elimination Half-Life of Antisense Drugs in Tissue. *Anal. Biochem.* 274: 241-248, 1999.

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ABSTRACTS AND PRESENTATIONS:

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PROFESSIONAL MEMBERSHIPS:

- 1) Society of Toxicology (SOT)
- 2) American Association of Pharmaceuticals Scientists (AAPS)
- 3) American Society for Clinical Pharmacology & Therapeutics (ASCPT)
- 4) Rho Chi Honor Society